UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/538,231	11/25/2005	Ofer Mandelboim	2488.019	8744

23405 7590 05/06/2009

HESLIN ROTHENBERG FARLEY & MESITI PC
5 COLUMBIA CIRCLE
ALBANY, NY 12203

EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
05/06/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,231	MANDELBOIM ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19 and 21-44* is/are pending in the application.

4a) Of the above claim(s) *6-18, 24-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,19 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 2/24/09 has been entered.

Group I, claims 1, 3-5, 19, 21-23, SEQ ID NO:4, species immunoglobulin, are examined in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 1, 3-5 remain rejected under 35 U.S.C. 103(a) as being obvious over Pende et al, 1999 (J Exp Med, 190(10): 1505-1516, IDS of 02/13/06), in view of Mandelboim et al, Nature, February 2001, 409: 1055-1060, for reasons already of record in paper of 09/24/08.

The response asserts as follows:

The Examiner takes the position that on the one hand, it is not germane whether or not Mandelboim et al fails to teach lysis of cancer cells by NKp46D2-Ig and NKp30- Ig conjugates via a macrophage dependent mechanism not involving NK cells, "because the claims are

composition claims and not method claims", and on the other hand, asserts that the NKp30-Fc conjugate of the subject application is obvious over Mandelboim et al and Pende et al in view of the teachings of those references regarding lysis of target cells by NK cells (pages 6-7 of the Office Action). The Examiner is dismissive of the Applicant's previous arguments relating to NK receptor-mediated cell lysis on the basis that the claims are not directed to methods, and yet has invoked arguments based on the very same NK cell lysis activity to allege obviousness of the claimed conjugate.

The response has been considered but is not found to be persuasive for the following reasons:

It is not germane whether or not Mandelboim et al fails to teach lysis of cancer cells by NKp46D2-Ig and NKp30- Ig conjugates via a macrophage dependent mechanism not involving NK cells, because the claims are drawn to compositions, and thus the reasons for making the composition, e.g.,whether or not the lysis of cancer cells by NKp46D2-Ig and NKp30- Ig conjugates is via a macrophage dependent mechanism not involving NK cells, do not have to be the same as that of the claimed invention.

The response asserts as follows:

Pende et al discloses that various monoclonal antibodies, including anti-CD 16, anti-NKp46 and the anti-NKp30 antibody AZ20, enhance the cell killing activity of fresh NK cells against certain targets, and that the enhancement reportedly involves cross- linking of NKp30 (Fig 4A and p. 1509, 2nd column, 2nd paragraph). The same AZ20 antibody is disclosed to inhibit NK cell-mediated cytotoxicity against other cancererous targets, and the inhibition

reportedly involves masking of NKp30 (Fig. 4B and p. 1510, 1st column), while an isotype-matched anti-CD56 antibody has no effect in any of the cell systems tested. No teaching is provided on how to distinguish between systems in which anti-NKp30 cross-links NKp30 versus those in which anti-NKp30 masks NKp30. Therefore, on the basis of Pende et al one of ordinary skill of the art would not be motivated to produce an NKp30-Ig conjugate on the basis of its ability to lyse cancer target cells with a reasonable expectation of success.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary to the response assertion, one would readily know which cancer cells are lysed by NKp30-Fc conjugate taught by the combined art. As clearly shown by Pende et al, the cancer cells used for testing whether NKp30 is necessary for lysis, by preincubation with an anti-NKp30 antibody, thus masking or blocking access to NKp30, are melanoma cells that **do not express** the **Fc receptor, FcγR** (the line before last line in figure 4 legend, on page 1510). On the contrary, the cancer cells used for testing target cell lysis, by crosslinking of NKp30 with anti-NKp30 antibody, are **positive for the Fc receptor**. It is noted that the presence of the Fc receptor is necessary for its binding to the Fc portion of the anti-NKp30 antibody and for efficient crosslinking of NKp30 mediated by FcγR, resulting in inducing of lyis of target cells, in view of the teaching of Pende et al. Pende et al teach that the F(ab')2 fragment of the antibody does not induce lysis, indicating that antibody-dependent NKp30 stimulation requires efficient crosslinking of NKp30 mediated by FcγR on target cells (p.1509, second column, paragraph before last). It is well known in the art that F(ab')2 fragment of an antibody does not have Fc portion.

The response asserts as follows:

The authors of Pende et al moreover raise the question of whether a correlation exists between ligand expression and susceptibility to NK-mediated lysis by different tumor cells (p. 1514, 2nd column, final sentence).

The response has been considered but is not found to be persuasive for the following reasons:

On page 1514, last paragraph, Pende et al teach as follows: "Based on the available data, it is possible to envisage a novel mechanism of tumor escape consisting in the downregulation (on tumor cells) of ligand molecules specifically recognized by NK-specific triggering receptors. Thus, the **identification** (emphasis added) of such ligands will allow the analysis of their distribution in normal versus tumor cells, and define whether a correlation exists between ligand expression and susceptibility to NK-mediated lysis by different tumor cells."

In the above paragraph, Pende et al refers to unknown ligands yet to be identified, not specifically to NKp30, and defining or studying of whether a correlation exists between expression of said ligands and susceptibility to NK-mediated lysis by different tumor cells.

The response further asserts as follows:

The deficiency of Pende et al is not remedied by Mandelboim et al. Mandelboim et al teaches that a direct interaction between NKp46 and haemagglutinin (HN) is involved in NK cell-mediated lysis, based on both binding experiments and cell lysis experiments. Fig 1 a shows that the binding of the conjugate NKp46-Ig is increased in cells transfected with HN, as compared to non-transfected cells. Cell lysis is not measured in the experiment of Fig. 1 a,

despite the general legend of Figure 1. Figs. 1 b and 1 c show that antibody directed against the conjugate NKp46-Ig i.e. "anti-NKp46 serum" inhibits NK cell-mediated lysis of the HN-transfected target cells. Similarly, Fig. 2 shows that anti-NKp46 serum inhibits lysis of IV-infected cells. However, in the experiments depicted in Figs. lb, lc and 2, no NKp46-Ig conjugate is present, and thus contrary to the assertion of the Examiner, the inhibition is not directed against the interaction between NKp46-Ig conjugate and HN, but rather against the interaction between NKp46 (expressed on NK cells) and HN.

Mandelboim et al provide no teaching or suggestion that the isolated conjugate NKp46-Ig has lytic activity. Accordingly, the title and the Abstract of the reference relate to recognition of HN by NKp46, NOT by NK-p46-Ig conjugate.

Moreover, Mandelboim et al actually teach away from using the combination of an NK receptor, such as NKp46, and an antibody to effect lysis of target cells. More specifically, the experiments depicted in Figures 1 b, 1 c and 2 involve incubation of NK GAL cells (expressing NKp46) with anti-NKp46 serum (i.e. an antibody), yet that combination results in diminished lysis, thereby teaching away from the presently claimed invention.

The response has been considered but is not found to be persuasive for the following reasons:

Contrary the response assertion, Mandelboim et al do not teach away from the claimed invention. Mandelboim et al teach that recognition or binding of haemagglutinin (HN) on target cells by NKp46 is required to lyse the cells, and this is tested by using NKp46-Fc in the experiments described in the reference (title, abstract, and in particular, p.1055, first paragraph after the Abstract, p.1056, second column). Figure 1b-c, its description on page 1056, second

column, first paragraph show enhanced NK-induced lysis of target cells by increased amount of haemagglutinin (HN) on cell surface, such lysis is inhibited by blocking the interaction between NKp46-Ig and NH, indicating that NKp46-Ig is necessary for NK-induced cell lysis.

Specifically, in addition to figure 1b-c legend, and abstract, Mandelboim et al explain figure1b-c as follows on page 1056, second column, first paragraph:

"**Pre-incubation** of a NK cell line, NK GAL, with a mouse **antiserum** raised against **NKp46-Ig** inhibited the increased killing of HN- transfected 293T cells, whereas incubation with a control serum had little effect (Fig. 1b). The same experiment revealed that each of the three HN-specific mAbs could block NK-mediated lysis, but a control mAb specific for CD99 had no significant effect (Fig. lc)". Mandelboim et al also teach that the anti-NH antibody **blocks the binding between NKp46-Ig and NH** on virus infected cells (page 1056, first column, first paragraph, last five lines, and table 1 on page 1056).

In other word, in view that: 1) NKp46-Ig binds to HN (abstract, p.1055, figure 1a, last three columns), and 2) preincubation of either an antiserum against NKp46-Ig conjugate or of an antibody against HN results in inhibition of the increased killing of the target HN- transfected 293T cells (figure 1b-c, page 1056, first column, first paragraph, table 1 on page 1056, supra), this indicates that **NKp46-Ig is necessary for NK-induced cell lysis** and that it is **the binding between NKp46-Ig conjugate and HN** in figure 1 that is blocked by the antiserum against NKp46-Ig conjugate or antibody against HN, resulting in inhibition of the increased cell lysis,. It is noted that increasing the amount of HN on target cell surface enhances the binding of NKp46-Ig to target cells, via its binding to HN (p.1055, first paragraph after the abstract). Thus, from the teaching of Mandelboim et al, it is clear that the NKp46-Ig conjugate is necessary for enhanced

NK-mediated lysis of target cells, such enhancement is via the binding of the NKp46-Ig conjugate to HN on target cells. When such binding is blocked by **preincubation** with either antibody against NKp46-Ig conjugate or anti-HN antibody, enhanced NK-mediated target cell lysis is inhibited.

One would have been motivated to replace NKp46 in the NKp46-Fc conjugate taught by Mandelboim et al with another member of the NCR family, NKp30, for making NKp30-Fc conjugate for lysis of target cancer cells by NK cells, in view that the conjugate NKp46-Fc by itself, without addition of a separate antibody, is required for enhanced lysis of target cells by a subset of NK cells, as taught by Mandelboim et al, and further in view that: 1) Crosslinking of NKp30 receptor is required to activate NK cell lysis of target tumor cells, as taught by Pende et al, and 2) NKp30, but not NKp46, is the main NK receptor that lyses some tumor cells, and also complements the action of NKp46 and/or NKp44 in some other tumor cells, as taught by Pende et al.

One would have a reasonable expectation that the NKp30-Fc conjugate would successfully trigger target cells lysis by NK cells, in view that crosslinking of NKp30 receptor by the Fc portion of a full length antibody is required to activate NK cell lysis of target tumor cells, as taught by Pende et al, which cross-linking would be expected to be successfully done by the Fc portion of the NKp30-Fc conjugate.

The response asserts as follows:

It would not have been obvious to use the extracellular domain of NKp30 to make the NKp30-Fc conjugate, in view that the NKp46-Fc conjugate of Mandelboim et al uses the

extracellular domain and in view that NKp30 belongs to the same Ig superfamily as NKp46. As is known by one of average skill in the art, the Ig superfamily comprises more than 200 related proteins having diverse functions, including for example antibodies, T cell receptor molecules, antigen presentation molecules, adhesion molecules, co-stimulatory molecules, and cytokine receptors. Many of these diversely functioning molecules are found on the same types of cells. Accordingly, the fact that NKp30 and NKp46 belong to the same superfamily does not render the conjugate fusion protein NKp30-Ig obvious over the prior art conjugate NKp46-Ig.

The response has been considered but is not found to be persuasive for the following reasons:

It is noted that NKp46 and NKp30 are two closely related molecules from a three member family of natural cytoxicity receptors (NCR) (Pende et al, p.1514, second column, second paragraph), both are triggering receptors involved in NK cell-mediated recognition and lysis of target cells, and both have similar structural organization (Pende et al, abstract, introduction on page 1505, p.1512-1513). Similar to NKp46, NKp30 protein also contains a signal peptide and an extracellular domain, forming an Ig-like domain of the V type, which domain contains two glycosylation sites (Pende et al, p.1512, first column, first paragraph). It would have been obvious to use the extracellular domain of NKp30, because extracellular domain of NKp46 has been successfully used in the conjugate of NKp46-Fc for inducing NK-mediated target cell lysis One would have a reasonable expectation of success in activation of NK-mediated lysis of target cells, because one would have expected that the extracellular NKp30-Fc conjugate would cross-link NKp30 receptors via its Fc portion and activates NK cell for lysis of target cells.

B. Claims 19, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pende et al, 1999, J Exp Med, 190(10): 1505-1516, IDS of 02/13/06, in view of Mandelboim et al, Nature, February 2001, 409: 1055-1060 as applied to claims 1, 3-5 above, and further in view of Sukhatme et al (US 6,797,488), for reasons already of record in paper of 09/24/08.

The response asserts as follows:

One of ordinary skill in the art would not be motivated to combine either or both of Pende et al and Mandelboim et al with Sukhatme et al to arrive at the claimed pharmaceutical composition with a reasonable expectation of success.

More specifically, Pende et al and Mandelboim et al both utilize a mammalian expression system (COS-7 cells) to produce recombinant proteins of interest, whereas Sukhatme et al uses a yeast expression system. One of ordinary skill in the art is aware that mammalian and yeast expression systems can yield substantially different results following expression of any particular recombinant protein, particularly with respect to post-translational modifications, such as in the glycosylation pattern of the protein product. These differences can have significant impact on the means by which a protein product may be formulated into a pharmaceutical composition.

Furthermore, Sukhatme et al actually teaches away from a fusion protein comprising the Fc portion of an immunoglobulin, as disclosed and claimed in the present application, and as taught by Mandelboim et al. More specifically, Sukhatme et al teaches a fusion protein of endostatin and IgG "specifically with the Fc portion removed" (Sukhatme et al, column 2, lines 59-67).

The response has been considered but is not found to be persuasive for the following reasons:

The reference by Sukhatme et al is cited for its use of **a pharmaceutically acceptable carrier** with a fusion protein. Sukhatme et al teach a composition in which the protein is combined with a pharmaceutically accepted carrier, and that such composition may also contain in addition to protein and a carrier, diluents, buffers etc.. (column 16, last paragraph, bridging column 17). The response has not shown, nor is there any indication that a protein produced from a mammalian system cannot be combined with a carrier for its storage in a buffer.

Further, whether the structure of fusion protein taught by Sukhatme et al is different from the fusion protein taught by Pende et al and Mandelboim et al, i.e, not containing Fc protein of the antibody, is not germane here, because the issue is the use of a pharmaceutically acceptable carrier with a fusion protein taught by Pende et al and Mandelboim et al.

It would have been primafacie obvious to one of ordinary skill in the art at the time the invention was made to combine the conjugate taught by Pende et al and Mandelboim et al with a pharmaceutically acceptable carrier, as taught by Sukhatme et al, for its storage.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, LARRY HELMS can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH-TAM DAVIS
April 30, 2009

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643